

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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22 GEN 1996

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NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

16. 01. 96

Applicant's or agent's file reference

HF 9428+9429

IMPORTANT NOTIFICATION

International application No.

PCT/EP 94/03182

International filing date (day/month/year)

23/09/1994

Priority date (day/month/year)

06/10/1993

Applicant

NICOX LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**
The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA



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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HF 9428+9429	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 94/ 03182	International filing date (day/month/year) 23/09/1994	Priority date (day/month/year) 06/10/1993
International Patent Classification (IPC) or national classification and IPC C07C203/04		
Applicant NICOX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


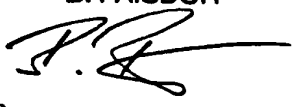
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 2 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 25/04/1995	Date of completion of this report 16. 01. 96
Name and mailing address of the IPEA  European Patent Office, P.B. 5818 Patentaan 2 NL-2280 HV Rijswijk - Netherlands Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer B. PAISDOR  Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

EP94/03182

I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed

☒ the description, pages 1 - 18, 20 - 31

pages

page 19

as originally filed

filed with the demand

filed with the letter of 10.10.95

☒ the Claims No. 1 - 9, 14 (part), 15 - 18

No.

No.

No. 10 - 14 (part)

as originally filed

as amended under Article 19

filed with the demand

filed with the letter of 10.10.95

☐ the drawings, sheets / fig.

sheets / fig.

sheets / fig.

as originally filed

filed with the demand

filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ pages:

☐ Claims No.

☐ drawings, sheets / fig.

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

EP94/03182**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty	Claims	1 - 18	YES
Inventive Step	Claims	1 - 18	YES
Industrial Applicability	Claims	1 - 10, 15 - 18	YES
	Claims	11 - 14	SEE BELOW

2. Citations and Explanations

2.1 The following documents have been considered for the purposes of this report:

D1 WO,A,94/12463
D2 WO,A,94/04484
D3 DE,A,2814556

2.2 Novelty (Article 33(2) PCT)

2.2.1 In document D3 substituted phenylacetic acid derivatives having anti-inflammatory activity is disclosed. The compounds of formula (I) of D3 can be compared with the structurally closely related compounds of the present claim 1, in which the group M of formula (IA) is represented by a group (XXXIII) wherein the substituent R is a group (X). In contrast to D3 the compounds of claim 1 of the present application are either esters or amides containing a nitric ester functional group of these acetic acid derivatives. Therefore claim 1 of this application represents novel subject-matter.

2.2.2 Consequently, the other independent (use) claims 11 - 14, the claims 15 and 16 pertaining to processes for the preparation of compounds of the principal claim, the claims 17 and 18 for pharmaceutical compositions containing the compounds of claim 1 and the remaining dependent claims 2 - 10 are also novel in the sense of Article 33(2) PCT.

2.3 Inventive Step (Article 33(3) PCT)

2.3.1 Document D3, which is considered to represent the most relevant state of the art, discloses (cf., e.g. page 23, table) substituted phenylacetic acid and phenylpropionic acid derivatives having anti-inflammatory and analgetic activity from which the subject-matter of claim 1 differs only in that it pertains to nitric esters of amide and/or ester derivatives of formula (IA). To show this distinguishing structural feature, example 1 of D3 (cf. page 24) can be compared with a compound according to claim 1 in which the groups A and B are hydrogen, n is 1, Y is oxygen and M represents a group (XXXIII) in which R represents a group (X).

2.3.2 The technical problem to be solved by the present invention may therefore be regarded as to provide **further** phenylpropionic and/or phenylacetic acid derivatives having anti-inflammatory and analgesic activity.

2.3.3 Nowhere in the prior art documents being currently on file an indication for a person skilled in the art can be found that nitric ester derivatives of the phenylpropionic acid compounds (for example) known from D3 might also possess the same pharmacological activities. Therefore an inventive step in the sense of Article 33(3) PCT is acknowledged for the compounds of claim 1.

2.3.4. Consequently, the claims 2 - 10 depending on claim 1 and the remaining independent claims 11 - 18 which refer to the preparation, and the application of the novel and inventive compounds according to claim 1 also represent inventive subject-matter.

2.4 For the assessment of the present claims 11 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

EP94/03182

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

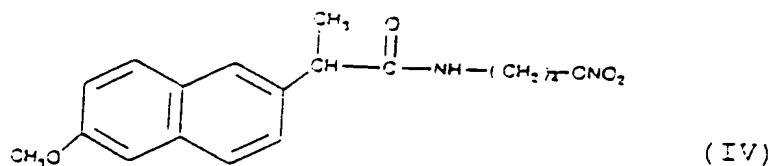
Application no. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO,A,94/12463	09/06/94	15/11/93	26/11/92
WO,A,94/04484	03/03/94	20/06/93	20/08/92

These documents **could** be relevant for the assessment of inventive step of the present application (cf. Rule 64(3) PCT).

WO,A,94/12463 (D1) discloses nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity; the groups Y, A and B of the compounds of general formula (I) (cf. D1, page 3) are the same as in this application. The meaning of the numeral n is identical and the substituent R² can be hydrogen or methyl as in the compounds of formula (IA) of the present claim 1. The distinguishing structural feature consists in the group R of D1 as can be shown by comparing, e.g. compound (XVIII) (cf. page 18 of D1) with example 1 of this application (cf. formula (IV), page 19).

In WO,A,94/04484 (D2) nitric esters of 2-(2,6-di-halophenylamino)phenylacetic acid also having, e.g. anti-inflammatory activity are disclosed. Again, the groups Y, A, B and the numeral n of D2 have the same meaning as in the present application. The comparison of e.g. compound (II) (cf. page 9, D2) with a compound according to claim 1 in which the group M represents a group (XXXI) and Y, A, B and n are the same as in formula (IV) (cf. page 19) shows that the distinguishing structural feature consists in the dihalophenylaminophenyl group of D2.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phthalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

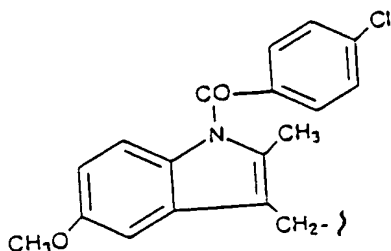
The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of ^{1.33 KPa} (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

AMENDED SHEET
IPEA/EP

n is equal to four.

10. Derivatives of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

The use of
11. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~
~~in the pharmaceutical field~~
as anti-inflammatory agents.

The use of
12. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~
~~in the pharmaceutical field~~
as analgesic agents.

The use of
13. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~
~~in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.~~

The use of
14. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~
~~in the treatment of the diseases of the cardiovascular system, in the treatment~~

AMENDED SHEET
IPEA/EP

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/EP 93/03193

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C203/04 A61K31/21 C07D333/22 C07D209/46 C07D491/04
 A61K31/40 A61K31/38 C07D207/337 C07D209/88 C07D333/24
 A61K31/16 C07C235/78 C07C235/34 C07C233/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 359 335 (CEDONA PHARMACEUTICALS B.V.) 21 March 1990 see page 4; claims ---	1,9
A	WO,A,92 01668 (ITALFARMACO S.P.A.) 6 February 1992 see claims ---	1,9
A	EP,A,0 300 400 (FUJISAWA PHARMACEUTICAL CO., LTD.) 25 January 1989 see claims ---	1,9
A	US,A,4 585 877 (C.A. DEMERSON ET AL.) 29 April 1986 see example 4 ---	1,7
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

4 February 1994

Date of mailing of the international search report

15. 02. 94

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Authorized officer

Bonnevalle, E

INTERNATIONAL SEARCH REPORT

nal Application No

PCT/EP 93/03193

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 988 728 (S.H.GERSON ET AL.) 29 January 1991 see the whole document ---	1,7
A	FR,A,2 612 185 (FARMITALIA CARLO ERBA S.R.L.) 16 September 1988 see page 12; claims -----	1,7,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/03193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0359335	21-03-90	NL-A- 8802276 AU-B- 638413 AU-A- 4133089 JP-A- 2134316 US-A- 5049694	02-04-90 01-07-93 22-03-90 23-05-90 17-09-91
WO-A-9201668	06-02-92	AU-A- 8097491 EP-A- 0540544	18-02-92 12-05-93
EP-A-0300400	25-01-89	AU-B- 623858 AU-A- 1919988 JP-C- 1666528 JP-A- 2028167 JP-B- 3031709 SU-A- 1706388 SU-A- 1760984 US-A- 4923886 US-A- 5010093	28-05-92 27-01-89 29-05-92 30-01-90 08-05-91 15-01-92 07-09-92 08-05-90 23-04-91
US-A-4585877	29-04-86	NONE	
US-A-4988728	29-01-91	NONE	
FR-A-2612185	16-09-88	AT-B- 392068 AU-B- 605253 AU-A- 1267988 BE-A- 1003280 CH-A- 675419 DE-A- 3807595 GB-A, B 2204579 JP-A- 63238058 NL-A- 8800575 SE-A- 8800846	25-01-91 10-01-91 08-09-88 18-02-92 28-09-90 22-09-88 16-11-88 04-10-88 03-10-88 11-09-88